Use of the sorption-desorption moisture transfer model to assess the utility of a desiccant in a solid product

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Summary

Desiccants are frequently included in moisture-sensitive solid pharmaceutical products to scavenge moisture in the package and prevent this water from interacting with the product. This study has demonstrated the utility of the sorption-desorption moisture transfer (SDMT) model for predicting moisture transfer between an aspirin formulation and a silica/carbon desiccant for defined masses of each component and their initial moisture contents. Furthermore, simulations were conducted that accounted for permeation of moisture into the container for three markedly different masses of formulation that correspond to 1, 75, and 1500 tablets with 0–2 g of desiccant. For this formulation/desiccant system, desiccant clearly had a marked effect in reducing the relative humidity inside the container for a significant time period for the single tablet and 75 tablet cases. However, the desiccant exhibited no practical effect in reducing relative humidity inside the container compared to formulation without desiccant for the 1500 tablet case. In conclusion, the SDMT model can account for the permeation properties of the package, the initial masses and moisture contents of the formulation and desiccant, and the total moisture sorption capacity of the formulation and desiccant to predict whether a desiccant will offer a significant moisture protective (i.e., reduced relative humidity inside the package) effect for a defined product.

Introduction

Desiccants are frequently included with moisture-sensitive products to protect them from water initially present following manufacture and packaging operations as well as from moisture permeating into the package over time. In theory, desiccants are placed in products to preferentially scavenge (sorb) moisture in the container such that this moisture is not available to interact with one or more components of a moisture-sensitive product. Pharmaceutical, food, textile, computer chip, and many other industries utilize desiccants to varying extents.

Several different types of desiccants are used. The first type of desiccant utilizes one or more water-soluble solutes and takes advantage of the ability of these materials to dissolve and form a saturated solution that yields a constant vapor pressure (water activity) above the solution. Since

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this is just vapor pressure lowering (a colligative property) at the saturated solution limit, the vapor pressure attained will depend on the number of species in solution per unit volume of water. Relative humidity within the package will be controlled as long as the solution remains saturated with respect to the components making up the desiccant. Use of this type of desiccant requires that the product and desiccant be physically separated due to the liquid water present in the vicinity of the desiccant.

A second approach is to use water-insoluble absorbents that have relatively large capacities to take up water per mass of solid. Such desiccants can be further subdivided into those that sorb water into their internal structure, and those that are porous in nature and scavenge water by capillary condensation into their porous structure. The utility of this type of desiccant is dependent on its mass, initial moisture content, pore size distribution for porous substances, and moisture sorption isotherm.

The current paper is applicable to water-insoluble absorbent-type desiccants and utilizes a previously developed sorption-desorption moisture transfer (SDMT) model (Zografi et al., 1988) to illustrate the underlying factors determining the manner in which moisture will distribute between a solid product (formulation) and the desiccant. In essence, the SDMT model accounts for all water initially in a system (i.e., in the vapor phase and sorbed to each component), the dry masses of each component, headspace volume, and moisture uptake isotherms for each component. Further, based on mass balance the SDMT model predicts a priori the final relative pressure (percent relative humidity/100) in a closed system. The current work utilizes the GAB (Anderson, 1946; Guggenheim, 1966; De Boer, 1968) equation to fit the isotherms of the formulation and desiccant, although other expressions fitting the data could also be employed. The GAB equation is expressed as:

$$W = \left\{ W_m C_g K (P/P^0) \right\} \times \left\{ \left(1 - K(P/P^0) \right) \right.$$

$$\left. \times \left(1 - K(P/P^0) + C_g K(P/P^0) \right) \right\}^{-1} \qquad (1)$$

where W is the amount of moisture sorbed to a component at a relative pressure, P/P^0; P denotes water vapor pressure, P^0 represents the saturated water vapor pressure at the temperature of the system; and W_m, C_g and K are constants obtained by fitting uptake data using a computer. The final SDMT (Zografi, et al., 1988) equation:

$$(P/P^0)^5 + C_1(P/P^0)^4 + C_2(P/P^0)^3$$

$$+ C_3(P/P^0)^2 + C_4(P/P^0) + C_5 = 0 \qquad (2)$$

is a fifth-order polynomial that is solely a function of P/P^0. Expressions for C_1–C_5 are available in Appendix 1 of Zografi, et al. (1988). Solving this fifth-order polynomial between 0 and 1 provides an estimate of the equilibrium relative pressure in the system following transfer of moisture between components. The SDMT model has been shown to predict final relative pressure very well in binary and ternary systems consisting of various combinations of microcrystalline cellulose, corn starch, gelatin capsules and silica gel (Zografi et al., 1988) and in a system of Mexitil® formulation and gelatin capsules (Kontny and Mulski, 1989).

Even though many products have been marketed containing desiccants, selection of the appropriate amount of desiccant used for a given product is usually determined by trial and error experimentation and has not been addressed in a rigorous manner in the literature. In this light, the first objective of this paper is to provide a fundamental method for determining an appropriate amount of desiccant (if any) for a solid product by accounting for the initial masses of the two solids (formulation and desiccant), their initial moisture contents, and their moisture uptake profiles in a closed system. Secondly, this paper will theoretically address permeation of moisture into a container and the effect this will have on the relative pressure inside the system.

Materials and Methods

Desiccant (United Desiccants, Gates Co., Camden, NJ), a 70:30 blend of White Sorb-It

(silica gel): Getter (carbon) was received in plastic polyethylene canisters. The contents of the canisters were emptied and used in moisture transfer studies. Aspirin tablets were used as an example of a typical pharmaceutical formulation that is moisture sensitive. The aspirin tablet formulation consisted of acetylsalicylic acid, pregelatinized starch NF, colloidal silicon dioxide NF, stearic acid NF, and Opadry® clear coating in a ratio of $325:75:2:4:4$. The tablets were manufactured by typical pharmaceutical procedures.

Water uptake isotherms

Moisture uptake isotherms were generated for the desiccant by emptying the contents of desiccant plugs into tared weighing boats, drying them in a vacuum oven at 0.1 Torr and 100°C, reweighing the boats and then equilibrating individual samples in desiccators over selected saturated salt solutions. Sample weight was monitored gravimetrically until no further change in weight was observed. Final moisture contents were obtained using thermogravimetric analysis (TGA) (Perkin Elmer TGS-2 Thermogravimetric Analyzer with 3600 Data Station, Ridgefield, CT) to ensure that all water was accounted for. TGA experiments were conducted over the temperature range 30–300°C at 10°C per min, with the water desorbing at approx. 150°C.

The water sorption isotherm for the aspirin formulation was obtained by equilibrating ground aspirin tablets in weighing boats over various saturated salt solutions in desiccators. Moisture uptake was determined gravimetrically. The formulation was not pretreated (i.e., dried) prior to storage to simulate practical situations in which a desiccant might be added to a product.

Moisture transfer studies

Equipment and procedures used for moisture distribution studies were similar to those described elsewhere (Grandolfi, 1987; Zografi et al., 1988; Kontny and Mulski, 1989). In essence, the system had high vacuum drying, temperature control and pressure measurement to 0.001 mmHg (Barocel® Type 600 Pressure Sensor and Type 1402 Electronic Manometer, Datametrics, Inc., Wilmington, MA) for water vapor and helium;

1×10^{-9} torr for vacuum (Granville-Phillips, Model 274 005 Ionization Gauge, Boulder, CO) capabilities. All headspace volumes were determined via helium (Linde Specialty Gases Division, Union Carbide Corp., Ultra High Purity Grade, Danbury, CT) gas expansions and associated pressure measurements.

Moisture transfer studies were designed to simulate transfer between approx. 75 aspirin tablets and 0.5, 1.0 or 2.0 g of desiccant. For practical reasons, experiments were conducted on a system where the desiccant and formulation (ground tablets) masses were scaled down by a factor of 10 (i.e., approx. 0.05, 0.1 or 0.2 g desiccant and 3 g of formulation). Desiccant and ground aspirin formulation were placed in separate compartments. Initial transfer studies began after the desiccant was dried under heat (100°C) and dynamic vacuum ($< 1 \times 10^{-4}$ mmHg) for at least 16 h and then reequilibrated at 20°C, the temperature at which all studies were carried out. The headspace volume in this cell was determined at this point. The aspirin formulation was exposed to dynamic vacuum pull for about 30 s to evacuate air from the system and then isolated. With the remainder of the system evacuated, water vapor of the desired relative pressure (using temperature controlled saturated salt solutions) was exposed to the aspirin formulation until no further change in vapor pressure occurred. Equilibrium was verified by isolating the saturated salt solution from the system and monitoring vapor pressure in the headspace above the formulation. If vapor pressure did change at this point, the cell was kept isolated until no further change in vapor pressure occurred. The two compartments were then equilibrated until an equilibrium pressure was attained. This pressure was converted to relative pressure by dividing by P^0 (17.535 mmHg at 20°C [Weast, 1986–87]). When multiple data points were generated on the same sample, the desiccant was isolated at the first pressure, while the aspirin formulation was equilibrated at another relative humidity. On average each equilibration took approx. 3 days (in vacuo). Only after all transfer studies were complete was the headspace volume measured above the aspirin formulation.

Results

Water sorption isotherms

Water sorption isotherms for the desiccant and aspirin formulation are presented in Fig. 1. The desiccant clearly sorbs more moisture at a given relative pressure than the formulation on a mass basis. For example, at 50% relative pressure the desiccant sorbs about 21% water, while the formulation only takes up about 2.2% moisture. Fig. 1 also illustrates the excellent fit of the GAB equation to both sets of sorption data over the entire relative pressure range.

Moisture transfer studies

Table 1 presents results of moisture transfer studies for systems with 0.05, 0.1 and 0.2 g of

TABLE 1

Predicted vs experimental moisture transfer between aspirin formulation and desiccant (mass of formulation = 3 g)

Mass of desiccant (g)	Initial relative humidity (%)		Final relative humidity (%)	
	Formulation	Desiccant	Experimental	Predicted
0.05	75.8	23.1	67.7	70.5
0.05	83.9	67.7	79.7	82.8
0.05	79.7	13.5	67.7	73.2
0.05	43.3	0.00	37.5	31.9
0.1	27.9	0.00	22.6	20.2
0.1	46.0	0.00	29.9	37.6
0.1	63.2	0.00	48.2	42.5
0.1	78.4	0.00	63.2	60.3
0.1	55.4	29.9	46.0	49.6
0.1	73.6	46.0	64.0	69.4
0.1	72.2	64.0	70.6	71.1
0.1	85.3	70.6	82.7	83.7
0.2	50.4	0.00	27.7	18.6
0.2	84.4	0.00	50.4	50.4
0.2	26.5	0.00	17.7	9.30
0.2	82.5	27.7	60.0	68.6
0.2	82.5	40.0	72.3	72.6
0.2	83.6	72.3	82.9	81.2

desiccant, respectively, and about 3 g of formulation. Such mass ratios correspond to systems of 0.5, 1 and 2 g of desiccant and approx. 75 aspirin tablets per container. Values calculated for the equilibrium relative humidity using the SDMT model are also presented. In all cases, agreement between theory and experimental results is quite good, demonstrating the utility of the SDMT model for predicting the final relative humidity for this system. Interesting to note are the resultant relative humidities after equilibration in the various systems for cases with different moisture contents of the desiccant prior to equilibration.
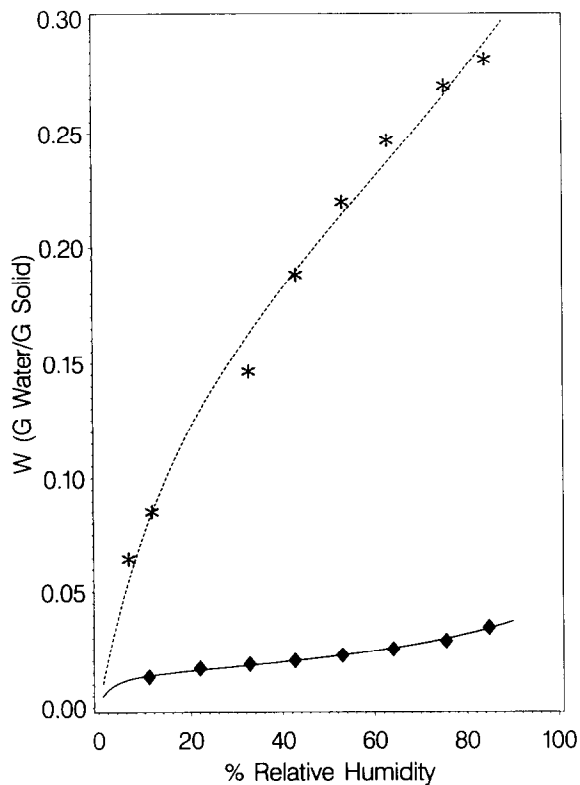

Fig. 1. Moisture uptake isotherm and GAB fits for desiccant and aspirin formulation. (*) Desiccant; (♦) aspirin formulation; (------) GAB desiccant; (———) GAB aspirin formulation; desiccant GAB values: $W_m = 0.2166$, $C_g = 11.53$, $K = 0.4189$; aspirin formulation GAB values: $W_m = 0.0149$, $C_g = 71.0$, $K = 0.6710$.

Discussion

Equilibration in a closed system

Several things appear clear from the previous results and calculations. The SDMT model appears applicable to the aspirin formulation/

desiccant system for predicting the final relative humidity for defined masses of formulation and desiccant, and their initial moisture contents. In addition, 2 g and less of 'dry' desiccant indeed reduces relative humidity in a closed system of 75 aspirin tablets. Several issues are still unclear however. First, can the SDMT model be utilized for this system to illustrate the relative benefit of increasing the mass of desiccant and decreasing initial moisture content of the formulation and/or the desiccant? Second, what is the effect of moisture permeation on relative humidity inside the package over time? Third, what is the effectiveness of a desiccant in reducing relative humidity where the ratio of mass of desiccant to mass of formulation changes markedly from that discussed above?
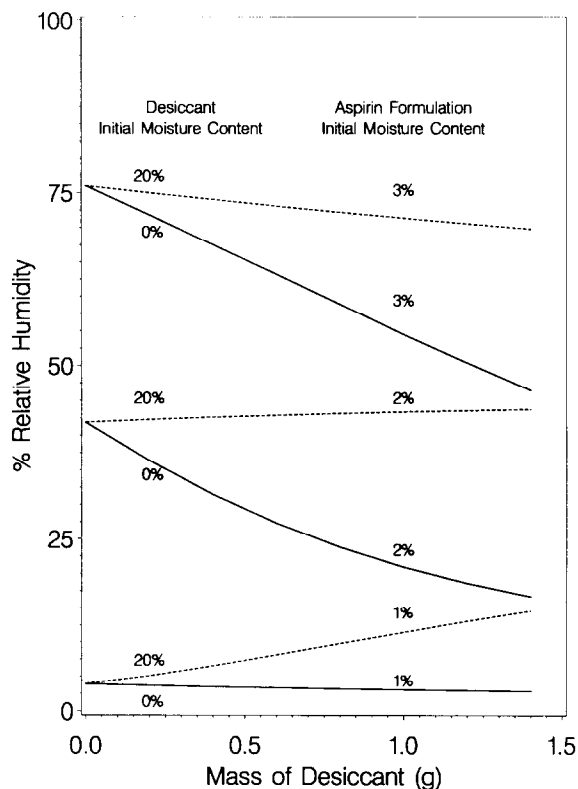

Fig. 2. SDMT-predicted % relative humidity as a function of mass of desiccant for aspirin formulation of various initial moisture contents (1–3%) and desiccant with initial moisture contents of 0 and 20%.

Fig. 2 shows the final relative humidities calculated from the SDMT model for a system of 75 aspirin tablets and 0–1.4 g of desiccant with the desiccant initially equilibrated at 0 and 20% moisture content, and the formulation initially equilibrated between 1 and 3% moisture content. Refer to Fig. 1 to correlate the initial moisture contents of the formulation and desiccant with the corresponding relative humidities at which these samples would be equilibrated. Note that the relative humidities in Fig. 2 for 0 g of desiccant correspond with the aspirin formulation relative humidities for a given moisture content. As desiccant is added, final relative humidity decreases for cases where the initial relative humidity associated with the desiccant is lower than that of the initial aspirin formulation relative humidity, while final relative humidity increases for cases where the initial relative humidity associated with the desiccant is greater than the initial formulation relative humidity. Also note the general increase in the final relative humidity profile in Fig. 2 as initial moisture content of the desiccant increases from 0 to 20% moisture content for an aspirin formulation of defined initial moisture content. This clearly shows the importance of using an initially 'dry' desiccant, containing as low an initial moisture content as is feasible, with moisture-sensitive solid products.

Equilibration with permeation – theory

The amount of moisture permeating into the package over a short time interval can be accounted for by the following expression

$$\int P_{\mathrm{m}}\left(\left(P/P^0\right)_{\mathrm{out}} - \left(P/P^0\right)_{\mathrm{in}}\right)\,\mathrm{d}t \qquad (3)$$

where P_{m} is the permeability constant of water into a given package, $(P/P^0)_{\mathrm{out}}$ represents the relative pressure outside the package, $(P/P^0)_{\mathrm{in}}$ is the relative pressure inside the package (calculated at time zero from the SDMT model (Zografi, et al., (1988)), and $\mathrm{d}t$ denotes a differential time increment. Note that P_{m} is defined for an entire package, and includes permeation through the walls of the container, through the cap and through the container/closure system. Approxi-

mating dt by a small time interval (such that the amount of moisture permeating into the package over that interval is much less than M_t, the total amount of moisture in the container) allows an approximation of the moisture permeating into the package using the SDMT model, where $(P/P^0)_{out}$ is maintained constant and $(P/P^0)_{in}$ is assumed not to change over the interval.

Once the amount of moisture permeating into the package is calculated for the time interval dt, this mass of water can be added to M_t (at $t = 0$) to obtain M_t ($t = 0 + dt$), the amount of water inside the container at the end of this time increment. Using M_t ($t = 0 + dt$) and assuming that equilibration of water with the solid components inside the container is fast relative to permeation into the container, the SDMT model can be
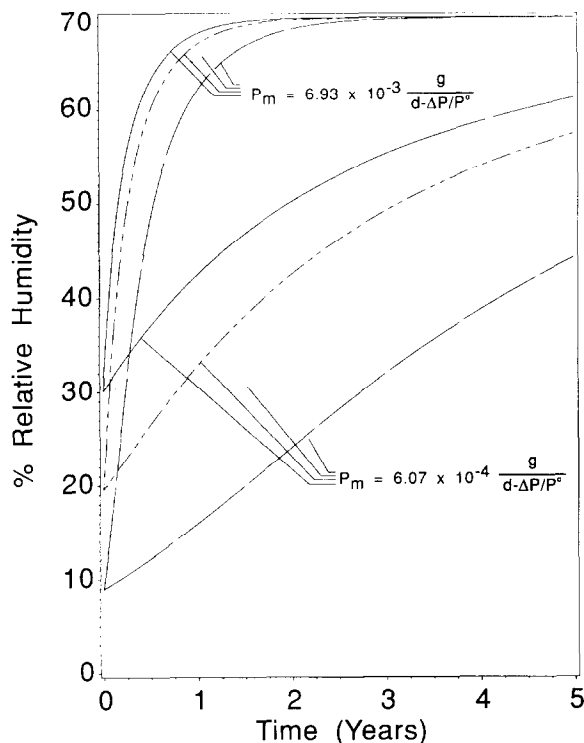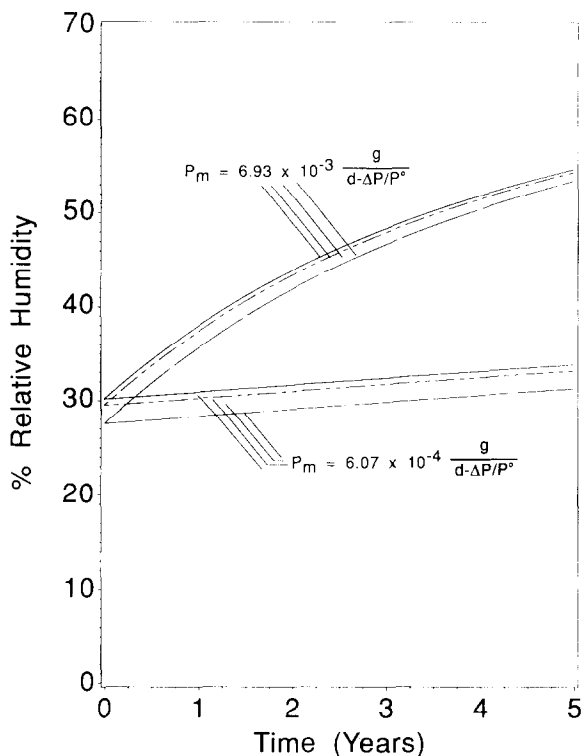

Fig. 3. Effect of container permeability and mass of desiccant on internal % relative humidity as a function of time for 75 aspirin tablets. Aspirin formulation initially equilibrated at 30% relative humidity and desiccant at 0% relative humidity. Mass of desiccant: (———) 0 g, (- - - -) 0.5 g, ($\cdots\cdots$) 1 g and (— — —) 2 g.

Fig. 4. Effect of container permeability and mass of desiccant on internal % relative humidity as a function of time for 1500 aspirin tablets. Aspirin formulation initially equilibrated at 30% relative humidity and desiccant at 0% relative humidity. Mass of desiccant: (———) 0 g, (- - - -) 0.5 g, ($\cdots\cdots$) 1 g and (— — —) 2 g.

utilized to obtain $(P/P^0)_{in}$ at a time equal to dt. This method can then be iterated to obtain $(P/P^0)_{in}$ as a function of time, where the time associated with a calculated $(P/P^0)_{in}$ is obtained by summing the dt intervals. Clearly, it is necessary to select a short dt for calculation purposes since the error introduced in calculating $(P/P^0)_{in}$ is cumulative. It was demonstrated that using time intervals of 0.5–10 days in the following simulations resulted in converging relative pressure vs time profiles. A similar iterative approach has been used previously (Gryziewicz, et al., (1988)). The primary advantage of this approach relative to others in the literature is that one can account for moisture distribution in systems of more than one solid component.

P_m will be characteristic of a particular system, including the materials, their thicknesses, total surface area, the closure system and the torque at which the closure is applied, and hence will be required to be measured for a given system. For purposes of discussion, consider that by USP standards a tight container will take up less than 100 mg/day per l due to moisture permeation with the container stored at 75% external relative humidity (20°C) and dry calcium chloride (i.e., 0% relative humidity) inside. Hence, the upper limit of permeation into a container would correspond to 6.93×10^{-3} g/(day $- \Delta P/P^0$) for a 1.75 ounce (oz) container. P_m expressed in this way is obtained by regression of moisture permeation rate vs $\Delta P/P^0$, defined as the difference in relative pressure inside and outside the container. For comparison, Gryziewicz (1988) reported a
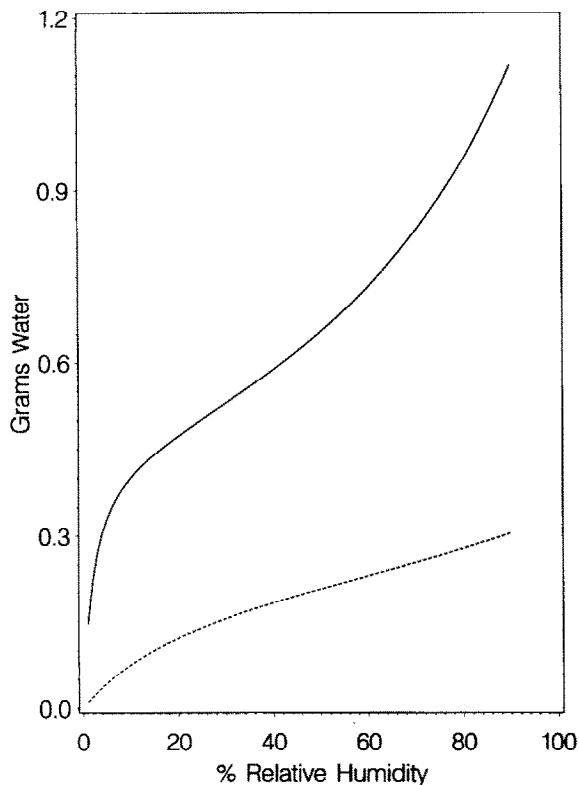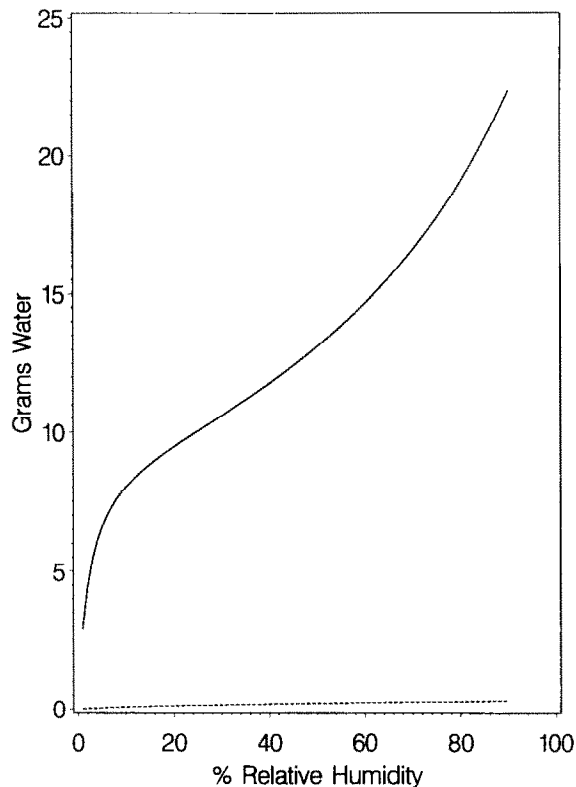

Fig. 6. Distribution of water between 1500 aspirin tablets and 1 g of desiccant as a function of internal % relative humidity. (———) Water sorbed to aspirin formulation; (- - - - -) water sorbed to desiccant.

value of 6.07×10^{-4} g/(day $- \Delta P/P^0$) for P_m into high density polyethylene bottles (1.75 oz) with a waxed glassine liner, pulp board spacer and metal cap applied with 15 inch pounds of torque. The value reported by Gryziewicz, et al. (1988) is about an order of magnitude lower than that defined as a tight container by USP standards. For further comparison, P_m values (in units similar to those described above) of 1.14×10^{-3} and 1.18×10^{-4} g/(day $- \Delta P/P^0$) can be calculated from data presented by Amidon and Middleton (1988) for PVC and PCTFE blister packages, respectively.

Equilibration with permeation; 75 tablets

Consider the system of 75 aspirin tablets and 0–2 g of desiccant described above, which might be typical of that used for clinical supply materi-

Fig. 5. Distribution of water between 75 aspirin tablets and 1 g of desiccant as a function of internal % relative humidity. (———) Water sorbed to aspirin formulation; (- - - - -) water sorbed to desiccant.

als. Fig. 3 shows simulations of the relative humidities inside the containers for P_m values of 6.93×10^{-3} and 6.07×10^{-4} g/(day $- \Delta P/P^0$), respectively, where the aspirin and the desiccant were initially equilibrated at 30 and 0% relative humidities, respectively, with the external relative humidity maintained at 70%. As expected, the initial relative humidities inside the containers are independent of P_m, but the relative humidities inside the containers increase at a considerably lower rate with an order of magnitude lower P_m.

Fig. 3 also shows the effect of increasing the mass of desiccant in this system for the two values of P_m, respectively. Whereas a system with a P_m
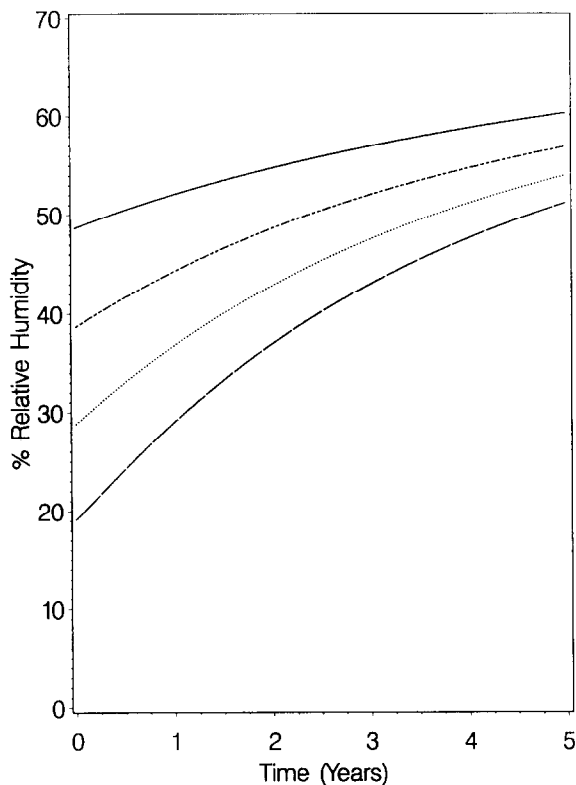

Fig. 7. Effect of drying 1500 aspirin tablets on internal % relative humidity as a function of time for a container with a $P_m = 6.93 \times 10^{-3}$ g/(day $- \Delta P/P^0$). Aspirin formulation initially dried to a relative humidity of: (———) 50%, (– - - –) 40%, ($\cdots\cdots$) 30% and (— — —) 20%. 1 g of desiccant initially dried to 0% relative humidity.
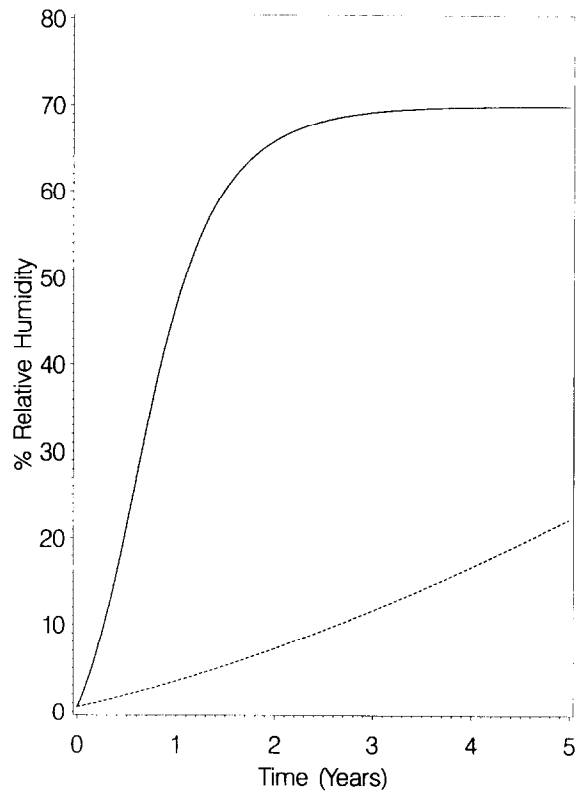

Fig. 8. Effect of blister package permeability, P_m, on internal % relative humidity as a function of time for 0.5 g of desiccant and one aspirin tablet. Aspirin formulation initially equilibrated at 30% relative humidity and desiccant at 0% relative humidity. $P_m = 1.14 \times 10^{-3}$ (———) and 1.18×10^{-4} (- - - - - -) g/(day $- \Delta P/P^0$).

of 6.93×10^{-3} g/(day $- \Delta P/P^0$) will extend the time to reach 50% relative humidity from 2 months to 7 months when using 2 g of desiccant relative to 0 g, the system with a P_m of 6.07×10^{-4} g/(day $- \Delta P/P^0$) extends this time period from about 2 years to over 5 years. This example clearly shows that a desiccant can help reduce the internal relative humidity for this system of 75 tablets provided the package also offers considerable resistance to moisture. Thus, defining packaging materials, closure systems and packaging line parameters that ensure sufficiently low permeabilities to moisture penetration are critical to protecting a moisture-sensitive product.

Equilibration with permeation; 1500 tablets

To address the effectiveness of a desiccant in controlling relative humidity inside the container for systems in which the relative mass of the formulation is much greater than that of the desiccant, consider a system of 1500 aspirin tablets and 0–2 g of desiccant. Fig. 4 shows the relative humidities inside the containers for P_m values of 6.93×10^{-3} and 6.07×10^{-4} g/(day $- \Delta P/P^0$), respectively, where the aspirin tablets and desiccants were again initially equilibrated at 30 and 0% relative humidities and the external relative humidity was maintained constant at 70%. As with the previous system, reduced P_m values result in lower rates at which relative humidities increase. Comparing Figs 3 and 4 shows that the

Fig. 10. Effect of mass desiccant on internal % relative humidity as a function of time for one aspirin tablet in a PVC/PCTFE blister package. Aspirin formulation initially equilibrated at 30% relative humidity and desiccant at 0% relative humidity. $P_m = 1.18 \times 10^{-4}$ g/(day $- \Delta P/P^0$). Mass of desiccant: (———) 0 g, (– – – –) 0.5 g, (······) 1.0 g and (— — —) 2.0 g.
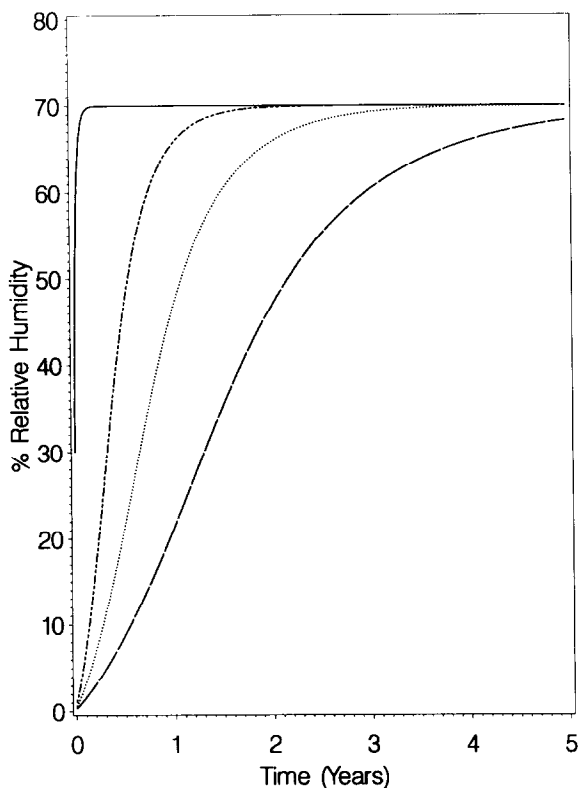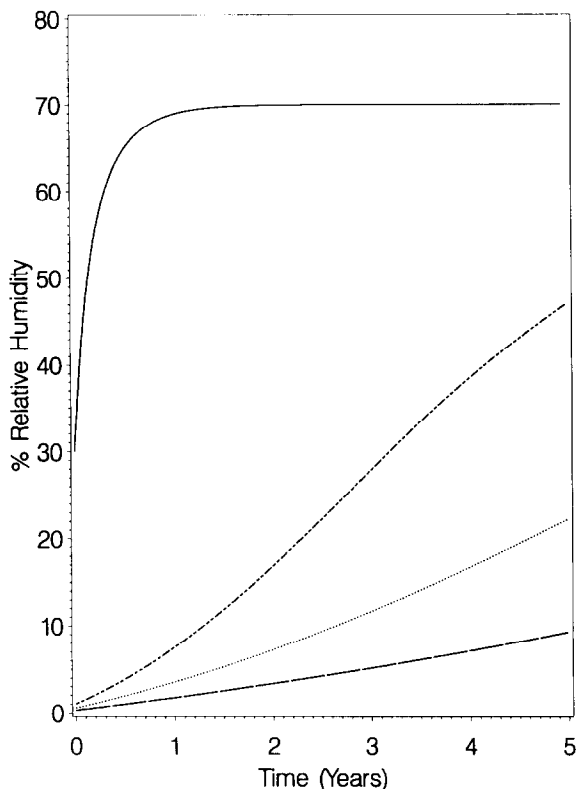

Fig. 9. Effect of mass of desiccant on internal % relative humidity as a function of time for one aspirin tablet in PVC blister package. Aspirin formulation initially equilibrated at 30% relative humidity and desiccant at 0% relative humidity. $P_m = 1.14 \times 10^{-3}$ g/(day $- \Delta P/P^0$). Mass of desiccant: (———) 0 g, (– – – –) 0.5 g, (······) 1.0 g and (— — —) 2.0 g.

mass of formulation also has a marked effect on the relative humidities inside the package.

Fig. 4 also illustrates that increasing the mass of desiccant in this system has little practical effect in controlling the relative humidities inside the containers for either value of P_m. The slightly lower relative humidities observed at a given time point with increasing mass of desiccant are due to the initial lowering of the relative humidities inside the containers. Figs 5 and 6 explain this quite well. Whereas Fig. 5 shows that 1 g of desiccant has a moisture sorption capacity at a given relative humidity of the same order of magnitude (about 3 times less) as the total mass of 75 aspirin tablets, Fig. 6 illustrates that the moisture

sorption capacity of 1500 tablets is significantly greater than 1 g of desiccant. In the latter case, the formulation acts as the primary moisture sink. Clearly, the capacity of the desiccant is dominated by the formulation in this case and suggests that the utility of a desiccant is negligible in such a system. Even with a P_m equivalent to the maximum limit allowed for a tight container by USP standards, Fig. 4 shows that the relative humidity will not attain a value of 50% until approx. 3.5 years. For this type of system, which might be considered an example of a commercial size pharmaceutical package in terms of number (mass) of tablets, the effect of drying the formulation will also have a major impact on the time necessary for the internal relative humidity to reach a certain level (e.g., 50%). Fig. 7 shows this effect for this system where the 1500 tablets are dried to initial relative humidities of 50, 40, 30 and 20%, respectively, and the desiccant to 0% relative humidity prior to packaging. Corresponding time periods to reach 50% relative humidity for a $P_m = 6.93 \times 10^{-3}$ g/(day $- \Delta P/P^0$) are 3 months, 3 years, 4.5 years and > 5 years, respectively. For such a system that exhibits sensitivity to moisture at or near 50% relative humidity, a tight moisture specification for the final tablet is warranted.

Equilibration with permeation; 1 tablet

At the other extreme, consider a system consisting of a single aspirin tablet packaged with 0.5 g of dry desiccant (i.e., initially 0% relative humidity) in PVC and PVC/PCTFE blister packages, similar to those employed by Amidon and Middleton (1988). Again assume the external relative humidity is constant at 70%. Fig. 8 simulates the relative humidities that would occur inside these systems as a function of time. Clearly, the PVC/PCTFE packaging system is superior to a similar blister package without the PCTFE laminate. Whereas the system with a P_m of 1.14×10^{-3} g/(day $- \Delta P/P^0$) attained an internal relative humidity of 50% at about 12 months, the laminated system with a P_m of 1.18×10^{-4} g/(day $- \Delta P/P^0$) only reached a relative humidity of 20% at 5 years. Figs 9 and 10 show the effect of increasing the mass of desiccant from 0 to 2 g

in this system with P_m values of 1.14×10^{-3} and 1.18×10^{-4} g/(day $- \Delta P/P^0$), respectively. Note the very fast equilibration with external relative humidity (70%) with no desiccant in Fig. 9 and the significant reduction in internal relative humidity as mass of desiccant is increased in Figs 9 and 10. In Fig. 9, the time to reach 50% relative humidity is increased from about 1 week with 0 g of desiccant, to about 6 months, 1 year and 2 years with 0.5, 1.0 and 2.0 g of desiccant, respectively. The simulation presented in Fig. 10 is even more dramatic. Whereas the system attains a relative humidity of 50% at about 2 months for a P_m of 1.18×10^{-4} g/(day $- \Delta P/P^0$) with no desiccant, the system reaches 50% relative humidity at about 5 years at 0.5 g and only 22 and 7% relative humidity, respectively, when the mass of desiccant is increased to 1 or 2 g.

Conclusions

(1) The SDMT model can be used to predict a priori the utility of a desiccant in controlling relative humidity for specific systems of known mass, moisture uptake profiles and container/closure permeability.

(2) In general, the SDMT model quantitatively illustrates the following:

(a) Desiccants have the greatest utility in controlling the relative humidity, and hence moisture content of individual components, inside the container in situations where the total moisture uptake capacity of the desiccant is greater than or at least of the same order of magnitude as that of the other components present.

(b) Use of packaging materials and closure systems that provide optimal moisture barrier protection (minimal permeability) is essential for maintaining reduced relative humidity inside the container for as long as possible for the case where the external relative humidity is greater than the internal relative humidity.

(c) Drying the formulation and desiccant to minimal levels prior to placing these components

inside the container will aid in establishing a low initial moisture level inside the container which will remain relatively low over time compared to initially higher levels.

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References

Amidon, G.E. and Middleton, K.R., Accelerated physical stability testing and long-term predictions of changes in the crushing strength of tablets stored in blister packages. *Int. J. Pharm.*, 45 (1988) 79–89.

Anderson, R.B., Modifications of the Brunauer, Emmett and Teller equation. *J. Am. Chem. Soc.*, 68 (1946) 686–691.

De Boer, J.H., *The Dynamical Character of Adsorption*, 2nd Edn, Clarendon, Oxford, 1968.

Grandolfi, G.P., Prediction of moisture transfer in mixtures of solids: Transfer via the vapor phase, M.S. Thesis, University of Wisconsin, Madison, 1987.

Gryziewicz, L.J., Jerzewski, R.L., Wong, T.M., Jain, N.B., Pazdan, J.L. and Cohen, E.M., Moisture permeation and equilibria in a high density polyethylene package. *Pharm. Res.*, 5 (1988) S258.

Guggenheim, E.A., *Applications of Statistical Mechanics*, Clarendon, Oxford, 1966.

Kontny, M.J. and Mulski, C.A., Gelatin capsule brittleness as a function of relative humidity at room temperature. *Int. J. Pharm.*, 54 (1989) 79–85.

United States Pharmacopeia (XXII) and National Formulary (XVII), US Pharmacopeial Convention, Inc., Rockville, MD, 1990, p. 1575.

Weast, R.C., *Handbook of Chemistry and Physics*, 67th Edn, Chemical Rubber Co., Cleveland, 1986–87, D-190.

Zografi, G., Grandolfi, G.P., Kontny, M.J. and Mendenhall, D.W., Prediction of moisture transfer in mixtures of solids: Transfer via the vapor phase. *Int. J. Pharm.*, 42, (1988) 77–88.